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Importance of Hepatitis C Virus RNA Testing in Patients with Suspected Drug Induced Liver Injury

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Summary

Background & Aims: The aims were to review the diagnosis, testing and presentation of acute hepatitis C (HCV) in patients initially diagnosed to have drug-induced liver injury (DILI) enrolled in the US DILI Network.

Methods: All patients with suspected DILI underwent testing for competing causes of liver injury and returned for 6-month follow-up. Causality was adjudicated by consensus expert opinion.

Results: Between 2004–2016, 1518 patients were enrolled and adjudicated and underwent 6 months of follow up. Initial locally acquired anti-HCV results were available in 1457 (96%), but

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HCV RNA in only 795 (52%). Stored sera were available for repeat testing, so that results were available on all 1518 patients (1457 for anti-HCV and 1482 for HCV RNA). 104 subjects (6.9%) had evidence of HCV infection- 10 positive for HCV RNA alone, 16 for anti-HCV alone and 78 for both. All 104 HCV-positive cases were reviewed and 23 cases were adjudicated as acute HCV. All presented with acute hepatocellular injury with median ALT 1448 U/L, alkaline phosphatase 232 U/L and total bilirubin 10.8 mg/dL. 22 (96%) patients were jaundiced. While all 23 cases initially had been suspected of having DILI, 19 were adjudicated as acute HCV and not DILI at the 6 month follow-up; while 4 were still considered DILI.

Conclusions: 23 of 1518 (1.5%) cases of suspected DILI were due to acute HCV infection. We recommend that initial and follow up HCV RNA testing should be performed to exclude HCV in patients with acute hepatocellular injury and suspected DILI.

Keywords

Drug induced liver injury; acute hepatitis C; hepatitis C RNA

Introduction

The diagnosis of drug-induced lived injury (DILI) relies on three main criteria: elevated liver biochemistry tests with a compatible history of exposure to a prescription drug or over-the-counter product, including herbal and dietary supplements (HDS), often with a characteristic clinical signature; resolution or improvement upon stopping the agent; and exclusion of other causes of liver injury. As there is no specific biomarker of DILI, this last criterion is critical, particularly as DILI has a wide spectrum of clinical presentations that can mimic viral and autoimmune hepatitis, biliary tract disease, septicemia, ischemic liver injury, and malignancy amongst others[1].

Chronic hepatitis C virus (HCV) infection affects several million people in the United States[2], and there has been a recent increase in acute cases likely related to increasing injection drug use and the “opiate crisis”[3]. In addition, outbreaks of acute HCV infection continue to be reported after medical and surgical procedures in the health care setting[4–6]. The diagnosis and exclusion of acute and chronic hepatitis C are challenging in patients who present with suspected acute DILI. Serological markers for HCV infection, including HCV RNA and anti-HCV antibody, are reliable diagnostic markers but have several limitations in separating acute from chronic infection. Anti-HCV antibodies are usually used to exclude acute hepatitis C in a patient with acute liver injury, but it does not distinguish between acute, chronic or resolved hepatitis. Importantly, the absence of anti-HCV antibodies does not exclude acute HCV infection, as this antibody may be undetectable early during the course of acute infection. Tests for HCV RNA are valuable in distinguishing between active and resolved infection, but the presence of HCV RNA does not distinguish between acute and chronic hepatitis C, and it may no longer be detectable if tested late during the course of acute infection because about 30% of acutely infected patients spontaneously clear HCV and cure themselves. There have been approaches to discriminate acute from chronic HCV infection using sequence pattern[7,8] or antibody avidity[9], but none is currently established. Thus, reliable diagnosis of acute hepatitis C usually requires testing at two time points demonstrating seroconversion to anti-HCV reactivity, *de novo* development of HCV RNA,

or loss of HCV RNA during recovery. These limitations in the diagnostic markers for HCV infection are particularly challenging in making a diagnosis of DILI, rather than HCV infection.

The Drug-Induced Liver Injury Network (DILIN) is a National Institutes of Health (NIH)-funded multicenter observational cohort study that prospectively enrolls patients with suspected DILI in the United States. Eligible patients must meet predefined laboratory criteria and be enrolled within 6 months of DILI onset[10]. The diagnosis of DILI uses two methods: expert consensus and the Roussel Uclaf Causality Assessment Method (RUCAM)[11,12]. Both methods emphasize exclusion of other causes of liver injury, particularly viral hepatitis. Formal causality assessment is not undertaken until a 6 month follow up visit, and some patients enrolled in DILIN are subsequently determined not to have DILI but rather another diagnosis based on follow up testing and history[13]. The aim of the current analysis was to review the results of anti-HCV and HCV RNA testing and their diagnostic accuracy in patients enrolled into the DILIN study. Furthermore, after completing HCV RNA testing in previously untested patients, we reevaluated patients to determine how many patients may have had acute HCV infection that had initially been thought to be DILI-related.

Methods

Enrollment criteria:

The DILIN prospective study is a multicenter observational cohort study that enrolls patients with suspected DILI. Eligible patients must meet at least one of four predefined laboratory criteria on two consecutive blood draws at least 24 hours apart: (1) serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 5 times the upper limit of normal (ULN) or 5 times pretreatment baseline values, if abnormal; (2) serum alkaline phosphatase (Alk P) levels that ≥ times the ULN or 2 times the pretreatment value, if abnormal; (3) any elevation of ALT, AST or Alk P with a total serum bilirubin of ≥2.5 mg/dL, or (4) any such enzyme elevations with an international normalized ratio (INR) greater than 1.5. Each subject must also be believed to probably have experienced DILI by the enrolling hepatologist. Subjects are required to be enrolled within 6 months of onset. Patients with acetaminophen hepatotoxicity, liver or bone marrow transplantation, autoimmune liver disease, sclerosing cholangitis or decompensated chronic liver disease are excluded. Patients with underlying hepatitis B or C, or nonalcoholic and alcoholic fatty liver disease are eligible, if the acute injury is believed to be superimposed DILI.

DILIN Study Design:

At the time of enrollment, patients undergo a medical history with details of drug or HDS exposure. Medical records are reviewed and data related to the liver injury are retrieved, including previous history of liver disease and HCV testing results. Additional laboratory testing is performed for other causes of liver injury that were not adequately excluded at the time of the initial evaluation. These assessments could include testing for hepatitis A, B, C, E, infectious mononucleosis, iron overload, and autoimmune conditions, as well as imaging for biliary tract disease[10]. In the case of hepatitis C, anti-HCV testing was routinely done If

not available from the medical records. In contrast, HCV RNA testing was performed at the discretion of the principal investigator at each center. In addition, a serum sample is obtained at study enrollment, aliquoted and stored at a central DILIN repository. Patients are asked to return for a follow-up visit at 6 months after enrollment, and those with persistent evidence of liver injury to return again annually for up to 4 years. The DILIN clinical sites and investigators are given in Supplementary Table 1.

Causality Assessment:

Enrolled subjects undergo a formal causality assessment process after their 6 month follow up visit. To elucidate the most likely cause of liver injury, two methods are employed: a consensus opinion by the DILIN Causality Committee made up of experienced hepatologists very familiar with DILI anda standardized RUCAM method calculated by the enrolling principal investigator. The DILIN causality system employs a 5-point likelihood score: 1 (definite: ≥ 95% likelihood), 2 (highly likely: 75%-94% likelihood), 3 (probable: 50%-74% likelihood), 4 (possible: 25%-49% likelihood) or 5 (unlikely: <25% likelihood); and the standardized RUCAM (8). By convention, RUCAM scores are grouped into likelihood levels as “excluded” (≤0), “unlikely” (1–2), “possible” (3–5), “probable” (6–8) and “highly probable” (≥ 9). In subjects in whom more than 1 agent is implicated, an overall causality score is assigned, and separate causality scores are assigned to each suspected drug or HDS.

Injury Assessment:

The pattern of liver injury is categorized using the R-ratio: [ALT/ULN] ÷ [Alk P/ULN], hepatocellular being defined by an R ≥ 5, cholestatic ≤ 2 and “mixed” between 2 and 5. A 5-point scale is used to define severity, ranging from 1 (mild, anicteric), 2 (moderate, jaundiced), 3 (moderate and hospitalized), 4 (severe, evidence of hepatic failure), and 5 (death or liver transplantation due to DILI within 6 months of onset).

HCV Testing:

In patients without locally obtained HCV RNA testing, stored serum samples were retrieved from the DILIN Repository and tested at Abbott Laboratories for HCV RNA using Abbott RealTi*m*e HCV assay (Abbott Molecular, Des Plaines, IL., lower limit of detection 12 IU/mL). All HCV RNA positive results were repeated for verification, and quantitative HCV RNA levels were obtained. Testing at the Abbott Laboratory was performed by persons without knowledge of prior HCV RNA or antibody results. Cases positive for anti-HCV antibodies or HCV RNA at the Abbott Laboratory were reviewed independently by 4 experienced hepatologists (JA, JHH, KRR, HLT), and the HCV status was categorized using predefined criteria as acute HCV, chronic HCV, resolved HCV, false-positive HCV serology, or unknown (Supplemental Material). Furthermore, with inclusion of results of the additional testing, the cause of the acute liver injury was re-adjudicated using a consensus approach as drug-induced, acute hepatitis C, exacerbation of chronic hepatitis C, or unknown. A diagnosis of acute hepatitis C required the presence of HCV RNA and one or more of the following: known *de novo* development of HCV RNA or seroconversion to anti-HCV, clearance of HCV RNA during follow up (in the absence of antiviral therapy), or compatible clinical and virologic course in a person in whom drugs were considered an unlikely cause of liver injury.

Some of the patients included in this analysis have been reported in prior publications from the DILIN prospective study[1,14]. The DILIN prospective study was approved by the Institutional Review Boards at each clinical site and data coordinating center and by a central Data Safety and Monitoring Board appointed by the NIDDK. All enrolled subjects provided written informed consent. The locations and principal investigators of the DILIN participating sites are given in the supplementary material.

Results

HCV testing of the total cohort:

Patients with suspected DILI enrolled in the prospective DILIN database between September 2004 and October 2016 with completed causality assessment and HCV testing results were included (Figure 1). Among 1734 patients enrolled, 1518 had undergone 6 months of follow up and formal causality adjudication by the time of the data analysis. Initial anti-HCV results were available on 1457 (96%) and HCV RNA results on 795 (52%) participants. Stored sera were available and selected from 814 subjects (127 of whom already had had HCV RNA testing that was repeated) and analyzed for HCV RNA. Thus, in total, HCV testing results were available on all 1518 adjudicated patients (1457 for anti-HCV and 1482 for HCV RNA).

HCV positive cohort:

Of the 1518 participants, 104 (7%) had evidence of current or past HCV infection: 10 were positive for HCV RNA alone, 16 for anti-HCV alone, and 78 for both (Figure 2). With the addition of these results, all 104 cases were re-reviewed in depth by 4 hepatologists and reassessed for causality as well as HCV status using standardized definitions and criteria (see above and supplementary material). The 104 cases with at least one positive HCV marker were scored by consensus as having acute HCV (n=23), chronic HCV (n=56), or resolved HCV (n=13) or as having false positive (n=2) or inconclusive results (n=10). Further analysis in this publication was confined to the 23 cases with evidence of acute hepatitis C.

Clinical Features of Acute HCV Cases:

The 23 cases of acute HCV infection included 9 women and 14 men, aged 20–83 (mean 47) years (Table 1). All presented with acute hepatocellular injury with median ALT 1448 U/L (range 458–3501), Alk P 232 U/L (range 92–551), and total bilirubin 10.8 mg/dL (range 1.1–23.1). The R ratios, calculated on the basis of initial ALT and Alk P values, were all above 5 and ranged from 5.3 to 40.7 (median = 18.6). The majority of patients had jaundice (96%), and most were hospitalized (78%). The course of disease was considered mild in 1, moderate in 20 and severe in 2 (with 1 fatality unrelated to liver disease).

The specific drug initially implicated in causing the liver injury and clinical features of each case are shown in Table 2. While all cases initially had been considered to have acute DILI, by the time of the original formal adjudication, 6 months later, 19 were judged to be due to HCV rather than DILI: At 6 months, 10 had been scored as unlikely [5] and 9 as possible [4]. The RUCAM calculated by the primary investigator was very variable but 11 cases

scored 6 or higher (probable or highly probable DILI). Only 4 patients had obvious risk factors for hepatitis C: 3 with injection drug use and 1 with high-risk sexual behavior. Interestingly, 7 patients had undergone an invasive surgical or dental procedure in the previous six months. Three patients had HIV co-infection.

The results and timing of the initial anti-HCV antibody and HCV RNA tests of the 23 acute HCV patients are shown in Table 3. Anti-HCV antibody was detected in 16 cases (70%) and HCV RNA in 22 (94%). The original anti-HCV antibody testing was all performed locally and was within a week of onset in 13 (57%), or within the following 2 months in 7 (30%) cases. Seven patients initially tested anti-HCV negative, one several weeks before onset (case 3); 4 were tested within the first week, and 2 were tested one and two months after onset. Four of these 7 were tested for HCV RNA locally and identified as having acute hepatitis C. The remaining 3 were not suspected of having HCV infection and were initially considered to have DILI, being identified as HCV RNA-positive only by the follow up testing at the Abbott Laboratory. A fourth patient, who was believed to have chronic hepatitis C with superimposed DILI, was later diagnosed as acute HCV infection based upon spontaneous clearance of HCV RNA on a follow up specimen. Thus, lack of HCV RNA testing at initial presentation would have missed evidence of HCV infection in 7 patients and lack of follow up would have misclassified at least one patient as having chronic rather than acute infection. In this cohort, all 23 patients with acute hepatitis C were initially believed to have DILI, although 19 were correctly identified once HCV testing was completed locally. Four additional patients [4/1518 = 0.26%] were misdiagnosed as having DILI but correctly identified once HCV RNA testing was performed on the research serum samples.

Discussion

The accurate diagnosis of DILI remains challenging in the absence of specific biomarkers and relies on thorough exclusion of other more common causes of liver injury. Laboratory studies in the work-up of DILI should include viral serology for hepatitis A, B and C and even hepatitis E in cases presenting with a clinical picture consistent with acute viral hepatitis[13]. It should also include assessment for other etiologies including alcoholic hepatitis, autoimmune hepatitis, biliary tract disease and depending on the clinical presentation, acute CMV, EBV, and HSV infection, the latter especially in subjects presenting with severe or fulminant hepatitis. In this cohort of1518 patients enrolled in the DILIN prospective study, 23 (1.5%) cases initially believed by experienced hepatologists to be due to DILI were actually due to acute HCV infection. All patients presented with hepatocellular injury and often a clinical presentation compatible with DILI. Furthermore, most patients did not have an identifiable parenteral risk factor for acute HCV infection, although 7 had undergone recent invasive procedures. The causality adjudication process in the DILIN is different from clinical practice where management decisions are typically made on a real-time basis. The RUCAM score is used to make a diagnosis of DILI but in this cohort was not very accurate as 11 of the cases had a RUCAM score of 6 or higher suggesting probable or highly probable DILI. This likely reflects that acute hepatocellular injury from drugs and hepatitis C have a very similar presentation and the lack of HCV RNA in half the cases may have impacted the score as one of the domains of the RUCAM requires exclusion of viral hepatitis. To maximize diagnostic accuracy, formal case adjudication in

DILIN occurs 6 months or more after enrollment, which allows for thorough testing and observance of clinical course. Hence, 19 of the 23 acute HCV cases identified here were not adjudicated as DILI when reviewed 6 months after onset. Nevertheless, analysis of archived serum samples revealed that 4 cases initially adjudicated as DILI after at least 6 months of follow up in fact had experienced acute HCV infection. Three of these cases were anti-HCV negative on study entry but had not been tested for HCV RNA locally and were found to be positive after testing of stored samples. A fourth case was belatedly diagnosed as acute hepatitis C based upon spontaneous clearance of HCV RNA detected at follow up. All 23 cases presented as acute hepatocellular injury compatible with acute viral hepatitis. The reason why drugs instead of HCV were initially considered the cause of liver injury was usually because of the lack of identifiable risk factors or the suspicion that positive HCV antibodies represented chronic HCV infection.

These data demonstrate that anti-HCV antibody testing is used in most centers to exclude HCV as a cause of acute hepatitis as it was tested in almost all patients. In contrast, testing for HCV RNA was done in only half of cases. The initial testing was done largely by the local physicians who referred cases to the DILIN investigators. Some patients were known to have chronic HCV before enrollment and were thought to have superimposed DILI. In others, the diagnosis of hepatitis C was not considered and testing for anti-HCV was not done until enrollment into DILIN, which might occur weeks or months after onset. Similarly, HCV RNA testing was occasionally delayed for several weeks or months after the suspected DILI onset. Such variability reflects the variability of HCV testing in clinical practice and evaluation of potential DILI.

In the entire DILIN prospective cohort[1], just over half of patients presented with acute hepatocellular injury, and about two thirds had jaundice. Not surprisingly, in these 23 acute HCV cases, all had hepatocellular injury and almost all had jaundice, but the other demographic factors such as age, sex, and race were similar to most patients that are enrolled as were the types of putative suspect drugs with antimicrobials accounting for 10 cases. The agents implicated initially in these 23 cases included many well-known causes of DILI, but often the phenotype of the injury was atypical, for example markedly hepatocellular injury after amoxicillin/clavulanate, intense jaundice and a long latency period and no immunoallergic features after fluoroquinolones. Other cases appeared to implicate agents that are after niacin, known but very rare causes of liver injury, such as escitalopram, naproxen, carboplatin, glipizide, and linezolid.

The limitations of this study deserve mention. HCV RNA testing was not available in all patients, and the local assays used to test for anti-HCV and HCV RNA were not uniform or applied from the same time points after onset. For instance, in one case (#23), HCV RNA was negative when tested locally but was repeatedly positive (in low titer) when rechecked centrally. In addition, some patients lacked testing at the appropriate times as in case #15 where the HCV RNA was drawn 7 weeks before DILI onset and case #8 where it was tested 24 weeks after onset. Other cases lacked any HCV RNA testing such that it was impossible to assign a confident diagnosis. Most patients did not have definitive evidence of acute HCV (documented negative serology before liver injury and evidence of seroconversion or development of HCV RNA). Nevertheless, only cases that fit strict consensus criteria for

acute HCV infection were included, so that the overall rate was, if anything, an underestimate. Among the 104 patients with positive HCV serology, results from 10 were considered inconclusive because the available results could not distinguish acute from chronic infection. Among the 23 patients diagnosed as having acute infection, only 11 had follow up testing from 6 months or more after onset, in whom with spontaneous clearance occurred in 6, while the remaining 5 appeared to go on to develop chronic hepatitis, 2 of who then underwent successful anti-viral treatment.

In conclusion, 23 (1.5%) patients believe by experienced hepatologists to have DILI had acute HCV infection that was diagnosed during follow-up. These patients all presented with hepatocellular injury, the majority had jaundice and most had no known risk factors for HCV infection. The diagnosis was only reliably made based upon HCV RNA testing which was positive in 7 subjects while they were anti-HCV negative at the time of their initial testing. These findings indicate that patients presenting with acute hepatocellular injury, even with features suggestive of DILI, should be tested for both anti-HCV and HCV RNA to reliably exclude acute HCV infection. Establishing the diagnosis of acute hepatitis C and careful follow up is all the more important now that safe and highly effective therapies are available for HCV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALT	Alanine aminotransferase
Alk P	Alkaline phosphatase
AST	Aspartate aminotransferase
DILI	Drug induced liver injury
DILIN	Drug Induced Liver Injury Network
HCV	Hepatitis C virus
INR	International normalized ratio
ULN	Upper limit of normal

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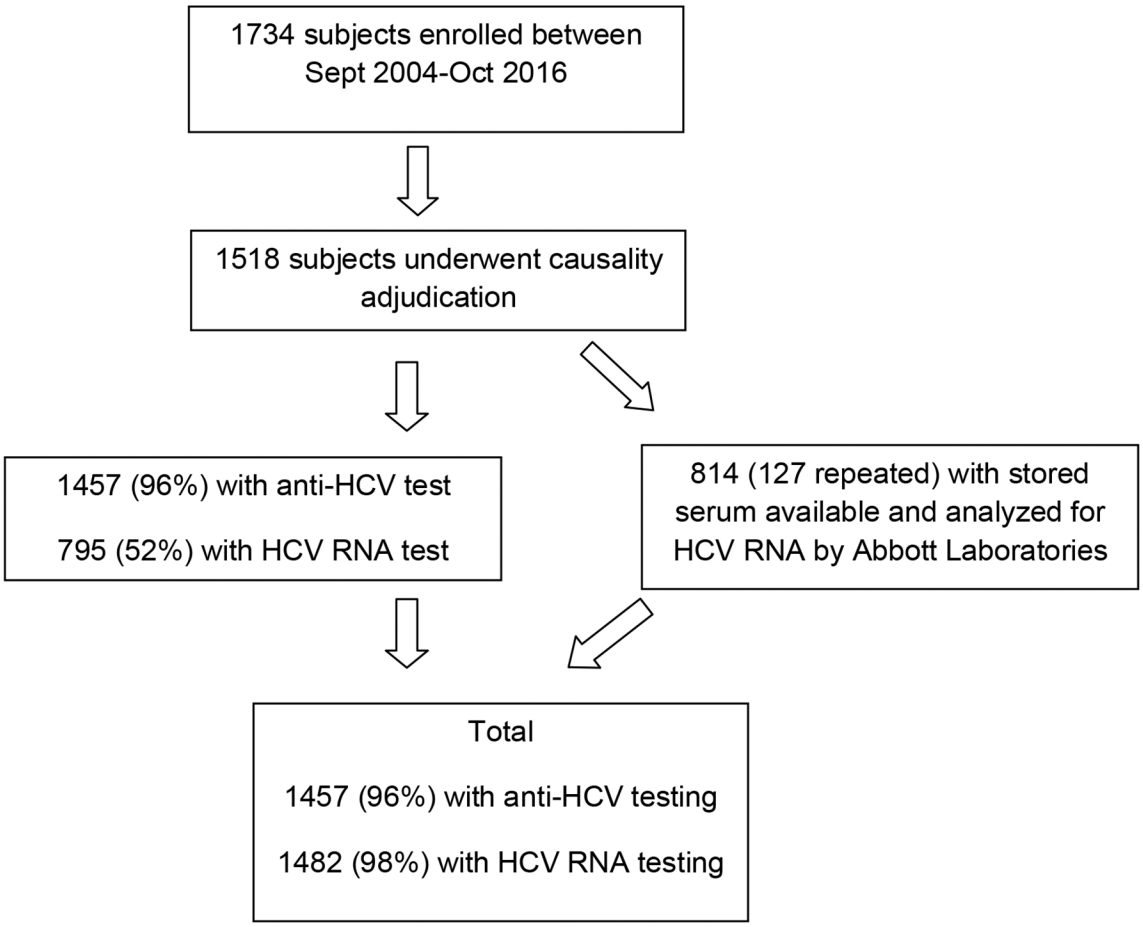

Figure 1.
Flowchart of 1734 subjects enrolled in DILIN prospective study with HCV testing

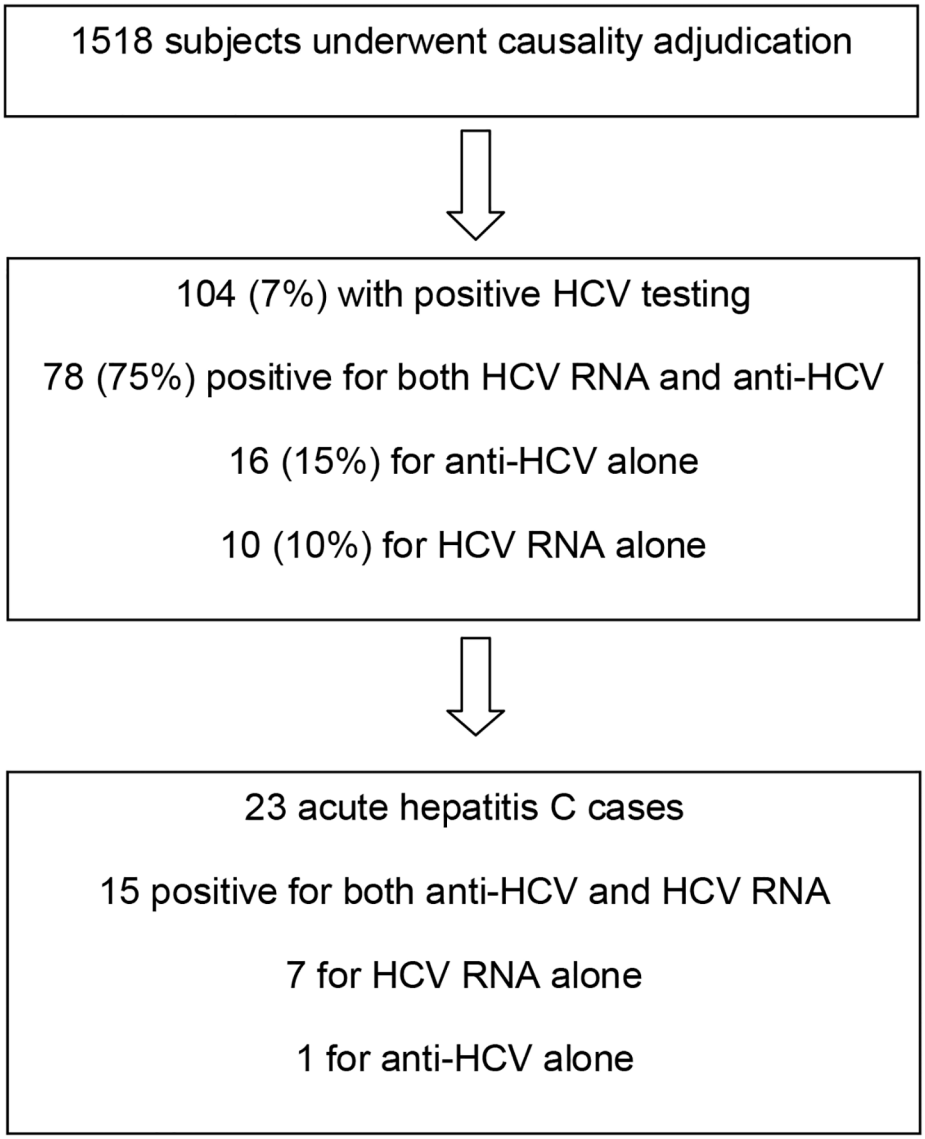

Figure 2.
Breakdown of 104 subjects in DILIN prospective study with positive HCV testing

Table 1

Clinical Features of 23 patients with acute hepatitis C

Feature	Units	Value or Number	Range or Percent
Median Age	Years	46	20 to 83
Male Sex		14	61%
White Race		21	91%
Median initial ALT	U/L	1448	458 to 3501
Median initial Alk P	U/L	232	92 to 551
Median initial total bilirubin	mg/dL	10.8	1.1 to 23.1
Bilirubin ≥ 2.5 mg/dL		22	96%
Median initial R ratio		18.6	5.3 to 40.7
Severity score			
Mild (1+)		1	4%
Moderate (2+)		4	17%
Moderate-hospitalized (3+)		16	70%
Severe (4+)		2	9%
Risk factor for HCV acquisition		4	23%
Anti-HCV negative initially		7	35%
HCV RNA done initially		19	83%
HCV RNA done in follow up at 6 months		11	48%

Table 2

Clinical Features of 23 acute HCV cases in the DILIN prospective cohort

Case	Suspected Drug(s)	Age [yrs]	Sex	Race	Peak ALT [U/L]	Peak Alk P [U/L]	Peak Bilirubin [mg/dL]	Causality score	RUCAM ***	HCV Risk factors
1	Fluconazole	53	F	W	2286	317	15.6	3	7	None
2	Topiramate	37	F	W	1591	179	13.4	5	8	None
3	Linezolid	39	F	W	1040	420	15.7	5	2	*None
4	Levofloxacin	64	M	AA	1236	468	18.2	4	3	None
5	Amoxicillin/Clavulanate	48	M	W	3378	551	7.8	4	8	None
6**	Efavirenz	40	M	W	458	221	2.5	5	1	High Risk Sex
7	Lovastatin/Niacin	57	M	W	3501	258	23.1	4	7	*None
8	Amoxicillin/Clavulanate	45	M	W	1448	234	10.8	4	6	*None
9	Escitalopram	49	M	W	2087	199	4.2	4	5	None
10	Carboplatin	83	M	W	1584	301	23.1	2	8	None
11	Celecoxib	44	F	W	802	224	13.1	5	4	*None
12	Buprenorphine/Naloxone	30	F	W	1852	167	6.2	4	7	IDU
13	Glipizide	62	M	W	1740	265	13.3	5	5	None
14	Levofloxacin	51	F	W	1869	372	18.3	5	5	None
15**	Rilpivirine	54	M	W	1809	299	6.7	5	2	IDU
16	Duloxetine	58	F	AA	662	92	3.4	4	8	None
17**	HIV Antivirals	43	M	W	607	341	13	4	6	None
18	Amoxicillin/Clavulanate	35	F	W	1289	192	5.8	5	5	*None
19	HDS	45	F	W	779	221	5.4	3	7	*None
20	HDS	50	M	W	1268	232	2.8	4	1	None
21	Naproxen	52	M	W	1451	137	10.1	3	8	*None
22	Baclofen	31	M	W	1444	119	12	5	−2	None
23	Cyclosporine	20	M	W	675	108	1.1	5	5	IDU

*No obvious HCV risk factor but surgical or dental procedures in the preceding few months

** HIV positive patients

*** RUCAM calculated by primary investigator

Abbreviations: IDU, injection drug use; HDS, herbal and dietary supplements; W, white or Caucasian race; AA, African-American or black race

Table 3

Timing of HCV Testing in 23 Acute HCV Cases in DILIN Prospective Study

Case	Anti-HCV result	Days from onset to anti-HCV test	HCVRNA result	HCV RNA titer [Log IU/mL]	Days from onset to HCV RNA test
1	Positive	0	Positive	1.87	7
2	Negative	0	Positive	3.22	8
3	Negative	−49	Positive	6.06	6
4*	Positive	19	Positive	5.54	0
5	Positive	5	Positive	5.41	5
6	Positive	91	Positive	7.05	91
7	Negative	31	Positive	NA	10
8	Positive	189	Positive	NA	2
9	Positive	33	Positive	4.74	19
10*	Negative	0	Positive	7.19	24
11	Positive	3	Positive	1.62	11
12	Positive	0	Positive	6.27	0
13	Positive	24	Positive	3.09	24
14	Positive	0	Positive	4.54	1
15	Positive	1	Negative	NA	−49
16	Positive	0	Positive	5.71	4
17	Negative	46	Positive	6.65	69
18	Positive	1	Positive	1.73	12
19*	Negative	0	Positive	5.66	7
20	Positive	14	Positive	6.58	23
21*	Negative	0	Positive	2.76	11
22	Positive	6	Positive	NA	9
23**	Positive	49	Positive	2.24	105

*HCV RNA not checked locally but stored serum was positive

**HCV RNA negative when checked locally at 105 days after DILI onset but stored sera from same time was positive when retested